TRICYCLIC ANTIDEPRESSANT

Amitriptyline

Elavil (US brand discontinued), available as generic

Tertiary-amine TCA with heavy antihistaminic and anticholinergic load, now used mainly for neuropathic pain, migraine prophylaxis, and insomnia.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
50-150 mg/day PO at bedtime	**10-28 h; active nortriptyline**	**CYP2C19, CYP2D6, CYP1A2, CYP3A4**	**Pain 1-2 wks; mood 4-6 wks**

⚠ FDA BOXED WARNING

Suicidal thoughts and behaviors: antidepressants increased the risk in children, adolescents, and young adults with major depressive disorder and other psychiatric disorders. Monitor closely for clinical worsening and emergence of suicidality, especially early in treatment and after dose changes.

INDICATIONS

- FDA-approved for major depressive disorder in adults and adolescents; the label does not establish safety in children under 12 years of age.
- Off-label first-line oral agent for painful diabetic neuropathy, postherpetic neuralgia, and other peripheral neuropathic pain syndromes.
- Off-label migraine and tension-type headache prophylaxis, where low bedtime doses of 10-50 mg are usually effective within 2 to 4 weeks.
- Off-label for fibromyalgia and centralized pain, generally combined with exercise and cognitive behavioral therapy rather than used alone.
- Off-label for chronic insomnia and for functional gastrointestinal disorders such as irritable bowel syndrome, at doses far below the antidepressant range.

DOSING & TITRATION

- Start **25 mg PO at bedtime** in healthy adults, or **10 mg** in older or frail patients, then increase by 25 mg every 3 to 7 days as tolerated.
- Usual antidepressant target is **50-150 mg/day**; outpatient maximum is **150 mg/day** and closely supervised inpatient maximum is **300 mg/day**.
- Neuropathic pain and headache prophylaxis usually respond to **10-75 mg** at bedtime, well below the doses needed for antidepressant effect.
- Supplied in the United States only as oral tablets of 10, 25, 50, 75, 100, and 150 mg; give the daily dose at bedtime to exploit the sedation.
- No formal renal adjustment exists, but use lower doses and slower titration in hepatic impairment because oxidative clearance is reduced.
- Taper by roughly 25 mg every few days when stopping to avoid cholinergic rebound with nausea, malaise, insomnia, vivid dreams, and akathisia.

MECHANISM OF ACTION

- Blocks presynaptic serotonin and norepinephrine reuptake transporters; the parent drug is more serotonergic and its metabolite nortriptyline more noradrenergic.
- Potent histamine H1 antagonism drives sedation, appetite stimulation, and weight gain, and underlies its usefulness at low bedtime doses for insomnia.
- Muscarinic M1 blockade produces dry mouth, constipation, urinary retention, blurred vision, tachycardia, and cognitive slowing in older adults.
- Alpha-1 adrenergic blockade causes orthostatic hypotension and falls, which is the main practical limit on titration in geriatric patients.
- Sodium channel blockade contributes to analgesia and also explains the QRS widening, arrhythmia, and seizures that dominate overdose presentations.

PHARMACOKINETICS

- Well absorbed orally with extensive first-pass metabolism; peak plasma concentrations occur roughly 4 hours after an oral dose and food has little effect.
- Elimination half-life is about 10 to 28 hours, permitting once-daily bedtime dosing, with steady state reached in approximately 4 to 5 days.
- Demethylated by CYP2C19 to nortriptyline, an active metabolite, then hydroxylated by CYP2D6; both enzymes carry clinically relevant genetic polymorphism.
- CYP2D6 poor metabolizers accumulate parent drug and hydroxy metabolites; CPIC advises a 50 percent dose reduction or selection of an alternative agent.
- Highly protein bound with a very large volume of distribution, so hemodialysis and forced diuresis do not remove meaningful amounts in overdose.

ADVERSE EFFECTS

- Anticholinergic effects are near universal, with dry mouth in over half of patients plus constipation, blurred vision, and urinary hesitancy.
- Sedation and weight gain are common and often dose limiting; orthostatic hypotension raises fall and fracture risk substantially in older adults.
- Dose-dependent slowing of cardiac conduction prolongs PR, QRS, and QT intervals and can provoke ventricular arrhythmia at supratherapeutic levels.
- Overdose is frequently lethal; ingestion above roughly **10 mg/kg** produces QRS widening, seizures, coma, and refractory hypotension within hours.
- Lowers seizure threshold, can precipitate mania in bipolar disorder, and may trigger acute angle-closure glaucoma or complete urinary retention.
- Sexual dysfunction, diaphoresis, and fine tremor are frequent; agranulocytosis and cholestatic hepatitis are rare but described in the label.

MONITORING

- Obtain a baseline ECG in patients over 50 years, in anyone with known cardiac disease, and before titrating above **100 mg/day** in any adult.
- Repeat the ECG after significant dose increases; a QRS above 100 ms or QTc above 500 ms should prompt dose reduction or discontinuation.
- Plasma levels are less well defined than for nortriptyline; a combined amitriptyline plus nortriptyline concentration of **100-250 ng/mL** is commonly cited.
- Draw levels for suspected toxicity, nonresponse at an adequate dose, questionable adherence, or known CYP2D6 or CYP2C19 variant status.
- Track weight, orthostatic blood pressure, bowel and bladder function, and suicidality closely during the first several weeks of treatment.

INTERACTIONS & CAUTIONS

- Contraindicated with monoamine oxidase inhibitors and within 14 days of stopping one because of hypertensive crisis and serotonin syndrome risk.
- The label contraindicates concomitant cisapride because of additive QT prolongation and the resulting risk of torsades de pointes.
- CYP2D6 inhibitors including fluoxetine, paroxetine, bupropion, and duloxetine markedly raise tricyclic levels and warrant dose reduction plus level checks.
- Additive QT risk arises with methadone, ondansetron, and class IA or III antiarrhythmics; anticholinergic load compounds with antihistamines and oxybutynin.
- Alcohol and other sedatives amplify central nervous system depression, and the drug blunts the antihypertensive effect of clonidine and guanfacine.

SPECIAL POPULATIONS

- Pregnancy data are broadly reassuring but limited; neonatal irritability, feeding difficulty, and transient withdrawal follow third-trimester exposure.
- Excreted into breast milk at low relative infant doses, though nortriptyline is generally preferred when a tricyclic is required during lactation.
- Safety in children under 12 years is not established, and adolescent use carries the class suicidality warning with mandatory close follow-up.
- The Beers Criteria list amitriptyline as potentially inappropriate at age 65 and older; if used at all, start at **10 mg** and titrate very slowly.
- Reduce the dose in hepatic impairment; no renal adjustment is specified, though hydroxy metabolites accumulate in advanced kidney disease.

PRESCRIBING PEARLS

- Nortriptyline delivers most of the analgesia with far less anticholinergic and orthostatic burden.
- A one to two week supply can be fatal; dispense small quantities to patients at suicide risk.
- Analgesic dosing is separate from mood dosing: **10-75 mg** at bedtime often controls pain.

References

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NOTE

References follow APA 7th edition style. Dosing, boxed warnings, and interaction data change; confirm every clinical decision against the current FDA prescribing information (DailyMed) and your institution's formulary. This sheet is an educational quick reference and does not replace the full label or clinical judgment.